Predictive Biomarker

**Abstract 1101P:**

Data cutoff: 07/15/2023.

The study was approved by Western Institutional Review Board, the central IRB for this study. The study was also approved by local IRBs at Memorial Sloan Kettering, MD Anderson, Ethicon, 3. University of Pennsylvania, Philadelphia, PA; USA; 4. Linnaeus Therapeutics, Haddonfield, NJ, USA; 6. Yale Cancer Center, New Haven, CT, USA; 6. Mass General Hospital Cancer Center, Boston, MA, USA; 7. Cedars Sinai Medical Center, Los Angeles, CA, USA; 8. University of New Mexico Cancer Center, Albuquerque, NM, USA; 9. Sidney Kimmel Cancer Center, Philadelphia, PA, USA; 10. START San Antonio, San Antonio, TX, USA; 11. Memorial Sloan Kettering Cancer Center, New York, NY, USA

**Background**

Metastatic Cutaneous Melanoma (mCM)

- Treatment-refractory mCM is an aggressive and lethal disease.
- Most mCM patients will progress on standard of care therapies and need further treatment.
- There is a large unmet need safe and effective therapies for treatment-refractory mCM.

**LNS8801**

- LNS8801 is an oral, selective, agonist of the G protein-coupled estrogen receptor (GPER).
- LNS8801 treatment results in increased melanocytic differentiation, reduced c-Myc protein levels in cancer cells, inhibited proliferation, suppressed invasion, and enhanced immune recognition.
- In preclinical models, LNS8801 has demonstrated increased activity in combination with immune checkpoint inhibitors (ICIs).

**Study Design**

- In the first-in-human dose escalation study, LNS8801 was safe and tolerable alone and in combination with pembrolizumab in patients with advanced solid tumors (NCT04130516).
- Monotherapy benefit has been demonstrated in mCM patients, including a patient that is on treatment for over 3.5 years with no evidence of active disease or recurrence by PET/CT.

**Primary Biomarker**

- There are relatively common germline variants of GPER, that result in amino acid substitutions and variant forms of GPER protein.
- Functional analyses of variant forms have suggested that they are hypofunctional.
- C refers to the consensus, normal form of GPER, and the V allele refers to the protein-coding variant forms, thus, a patient can be C/C, C/V, or V/V.

**Methods**

- In a post-hoc analysis, the C/C genotype of GPER had significantly improved PFS on LNS8801 therapy compared to patients with the C/V or V/V forms of GPER across tumor types and dosing regimens.
- These data suggest that patients with C/C germline GPER are having improved outcomes with LNS8801 treatment, and that C/C GPER is a likely predictive biomarker for LNS8801 efficacy.

**Efficacy Overview**

- Of the 10 patients evaluable for efficacy, 2 had partial responses, 5 had stable disease
  - ORR of 20% and DCR of 70% for all patients
  - Both patients with partial responses remained on treatment for >24 weeks.
  - Consensus germline GPER was present in 7 of 10 patients. Of 7 patients positive for this biomarker, 2 had partial responses and 3 had stable disease
  - ORR of 29% and DCR of 71%.

**Patient Level Details**

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**Conclusions**

- LNS8801 alone and in combination with pembrolizumab is tolerable without unanticipated toxicities.
- LNS8801 demonstrates encouraging anti-tumor activity in patients with iPD1 and cCTLA-4 refractory mCM, with an overall ORR of 20%, and biomarker positive ORR of 29%.
- These data support further development of LNS8801 in combination with pembrolizumab to treat mCM patients, especially for patients with consensus germline GPER (C/C).

This study was supported by Linnaeus Therapeutics and NCI SBIR Phase 2B BR44CA228695

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